Analytical Challenges and Learnings from Developing a Multi-stage Flow Process

A Chemists View
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Reaction Chemistry & Engineering
RSC INTEREST GROUP PROCESS CHEMISTRY AND TECHNOLOGY

Background

- I joined the pharmaceutical industry some 37years ago and through a series of moves and mergers ended up in process development.
- From 2000 I was mainly involved with kinetic analysis, process modelling and the development of continuous processes.

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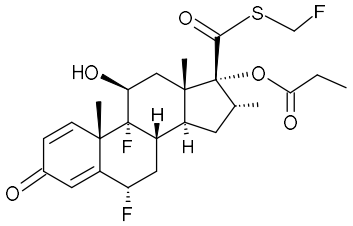
Introduction

- The activities described relate to the development of a flow process to Fluticasone Propionate (Flonase) however the challenges would be similar for any process redevelopment of an established product.



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Relevant Analytical Background

- Fluticasone Propionate (Flonase) was patented in 1980 and approved for use in 1990.
- Analytical specifications reflect the available technology of the time.
- Analytical methods for isolated intermediates in the synthesis were fit for purpose for controlling quality.
- Various in house physical property specifications were developed to assess batch suitability for different formulations

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Relevant Analytical Background

- The Drug substance release chromatography method had a 60 minute run time and was capable of resolving around 30 impurities.
- The methods for the intermediates were prone to artefacts if samples were left for some time.
- From a reaction monitoring and kinetic analysis perspective these methods left a lot to be desired as reaction samples would require multi-hour stability. However the drug substance method did prove valuable in tracking impurities through the process.

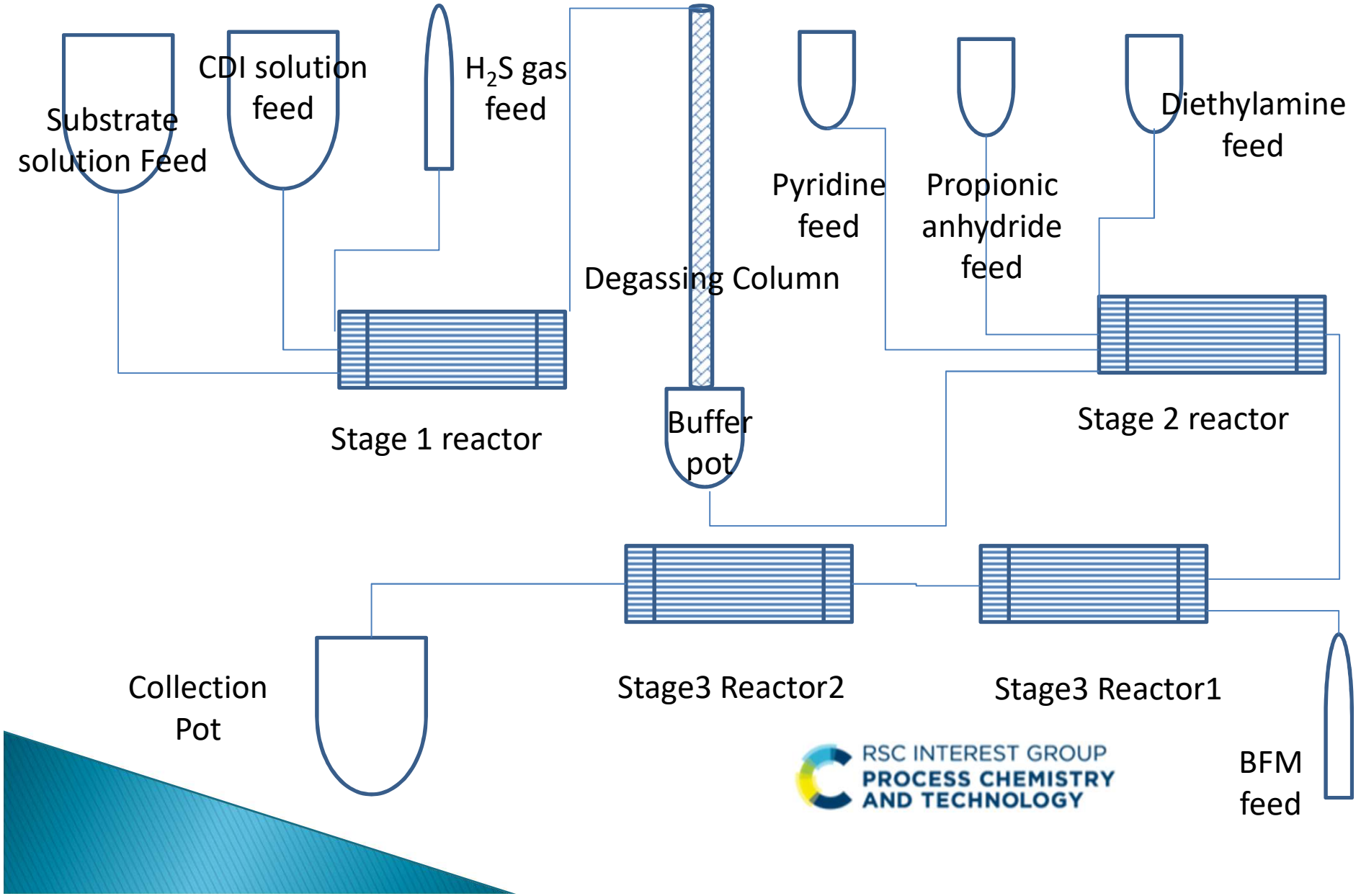
Challenges Due to flow Chemistry

- Unless the reactions are very fast an understanding of the reaction kinetics is essential in a flow process so a quantitative profile of the reaction vs time is required.
- The determination of solution concentrations in a dynamic system is significantly more challenging than end point determination.
- Typically a quench to generate a stable solution from which the reaction concentrations can be inferred is used.

Challenges Due to flow Chemistry

- Simple dilution (after all 10ul into 1ml typical sample prep is a 100fold dilution) may be adequate to slow the chemistry sufficiently for offline analysis assuming any Intermediates are stable to the analytical conditions
- In situ analysis with various analytical probes (eg ir, uv, conductivity, nmr) can yield valuable data but benefit from offline separation techniques to aid calibration and impurity profiling.

Process Schematic



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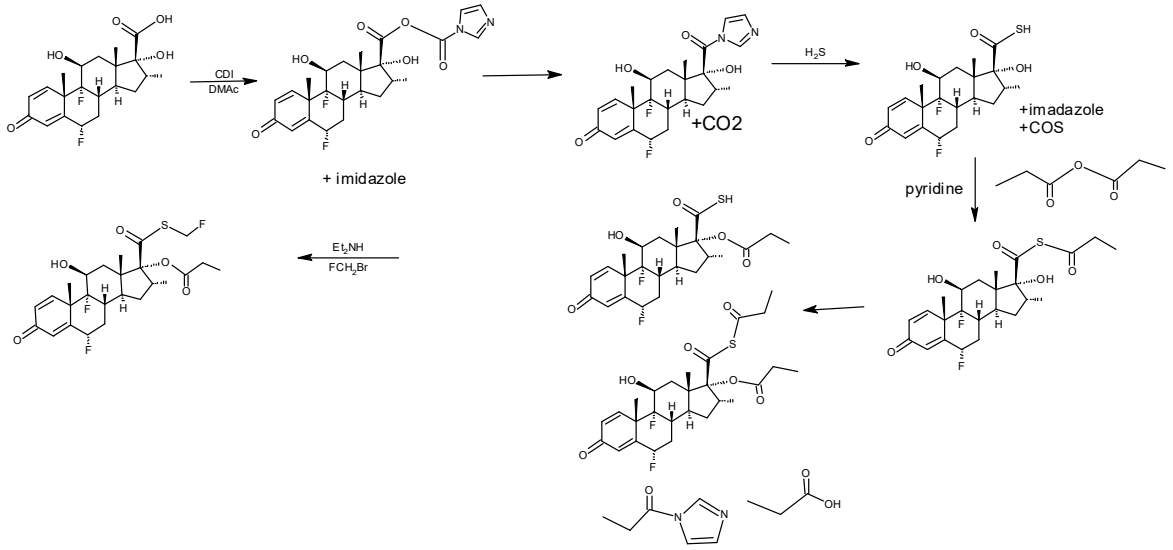
Stage 1 Chemistry



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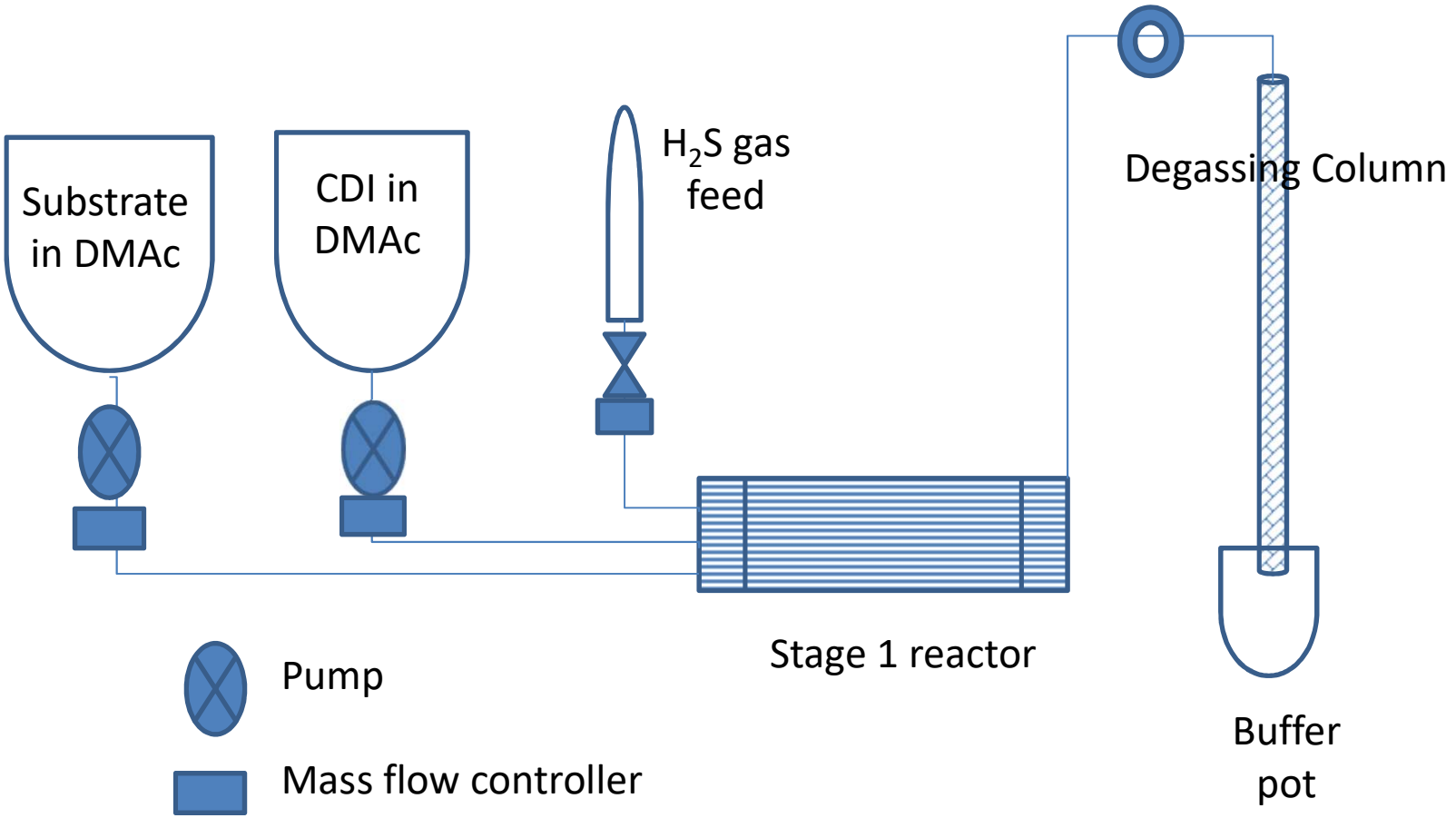
Process Schematic Stage 1



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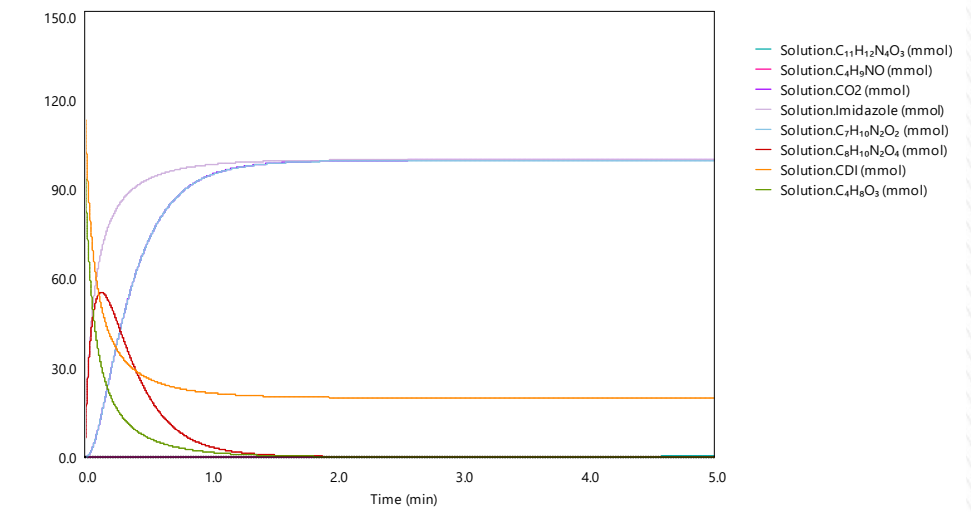
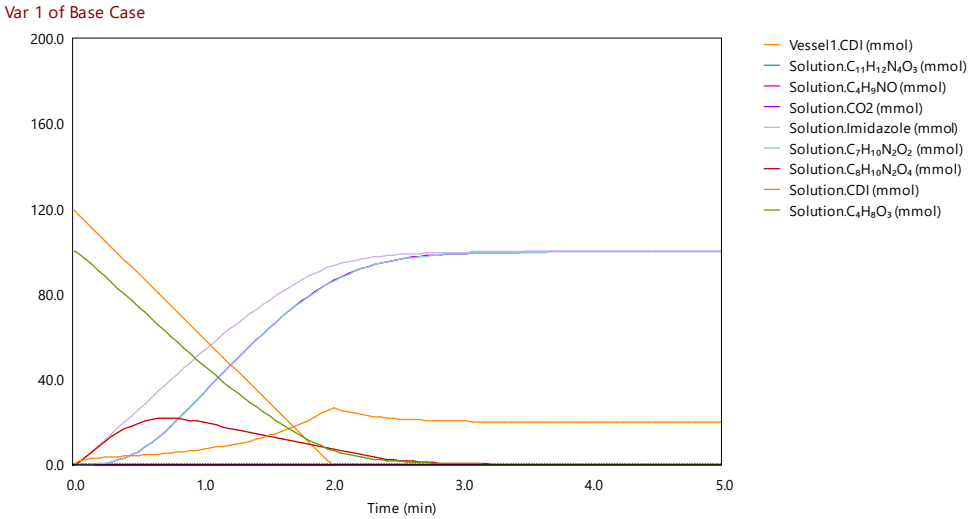
CDI Reaction Profile



Plug flow Reactor

Scale-up Systems



Batch Reactor
2minute Dosing

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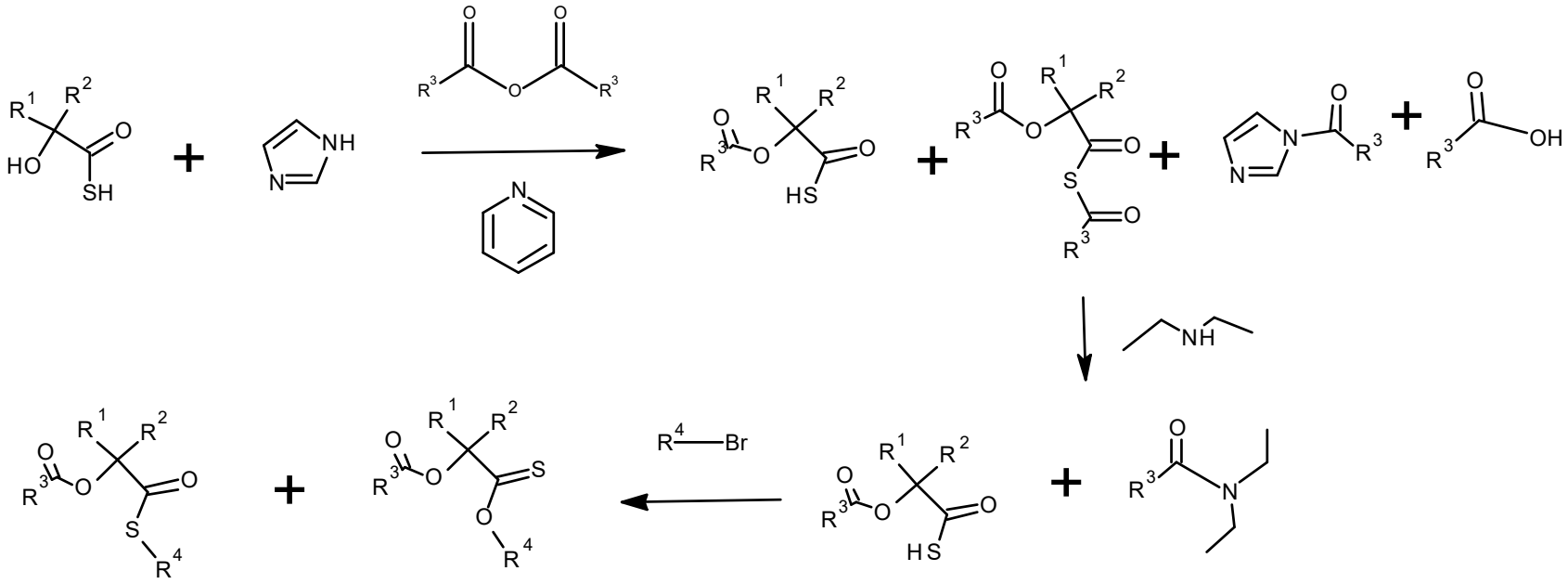
Stages 2 and 3



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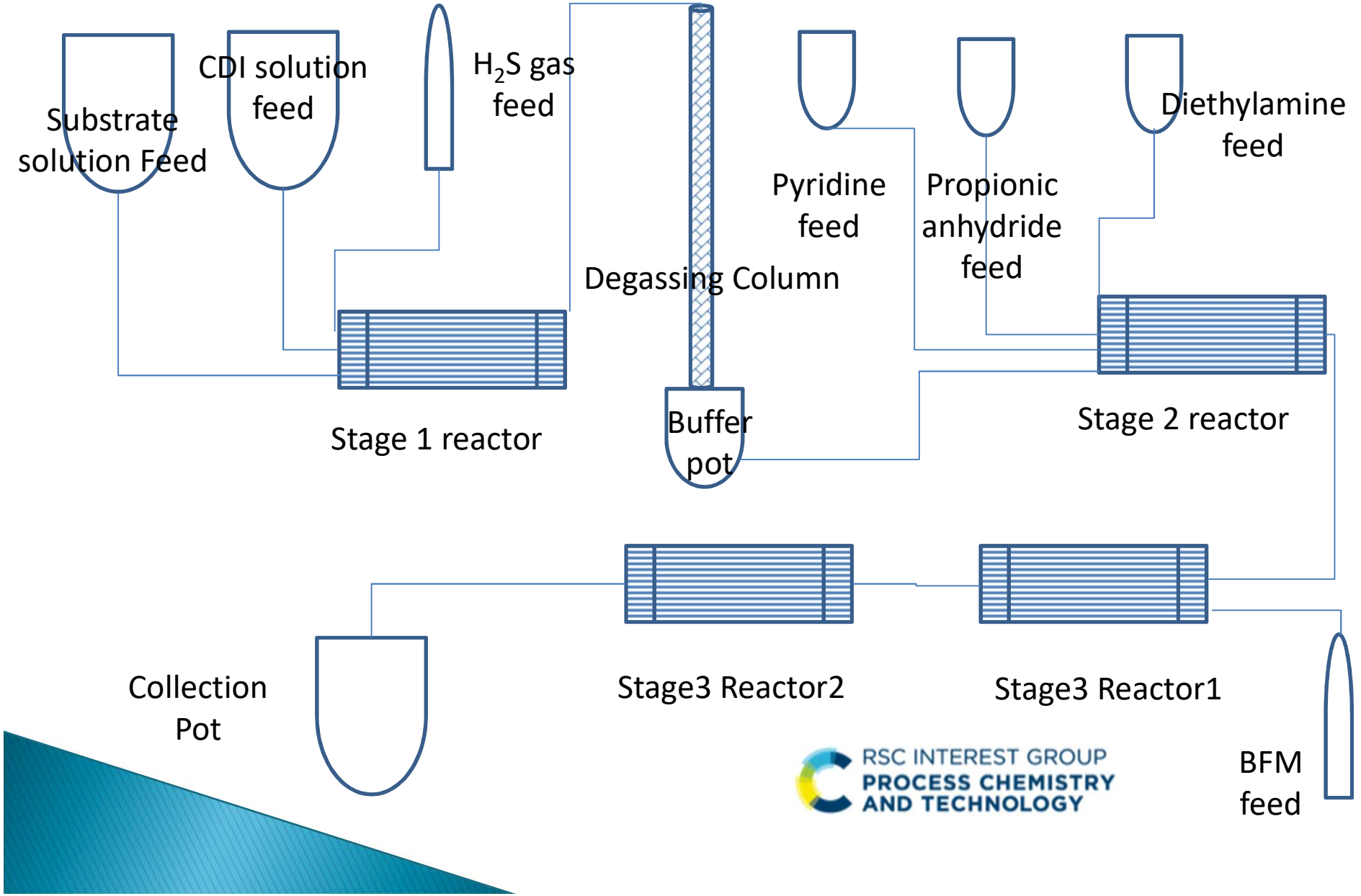
Process Schematic



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Telescoped Processes

For

- Reduced number of vessels used.
- Reasonable process velocity.

Against

- Complex from process instructions and operator point of view.
- Increased risk of maloperation.
- Probably require in process checks.
- Cause of process failure difficult to identify
- Need cleaning verification between batches

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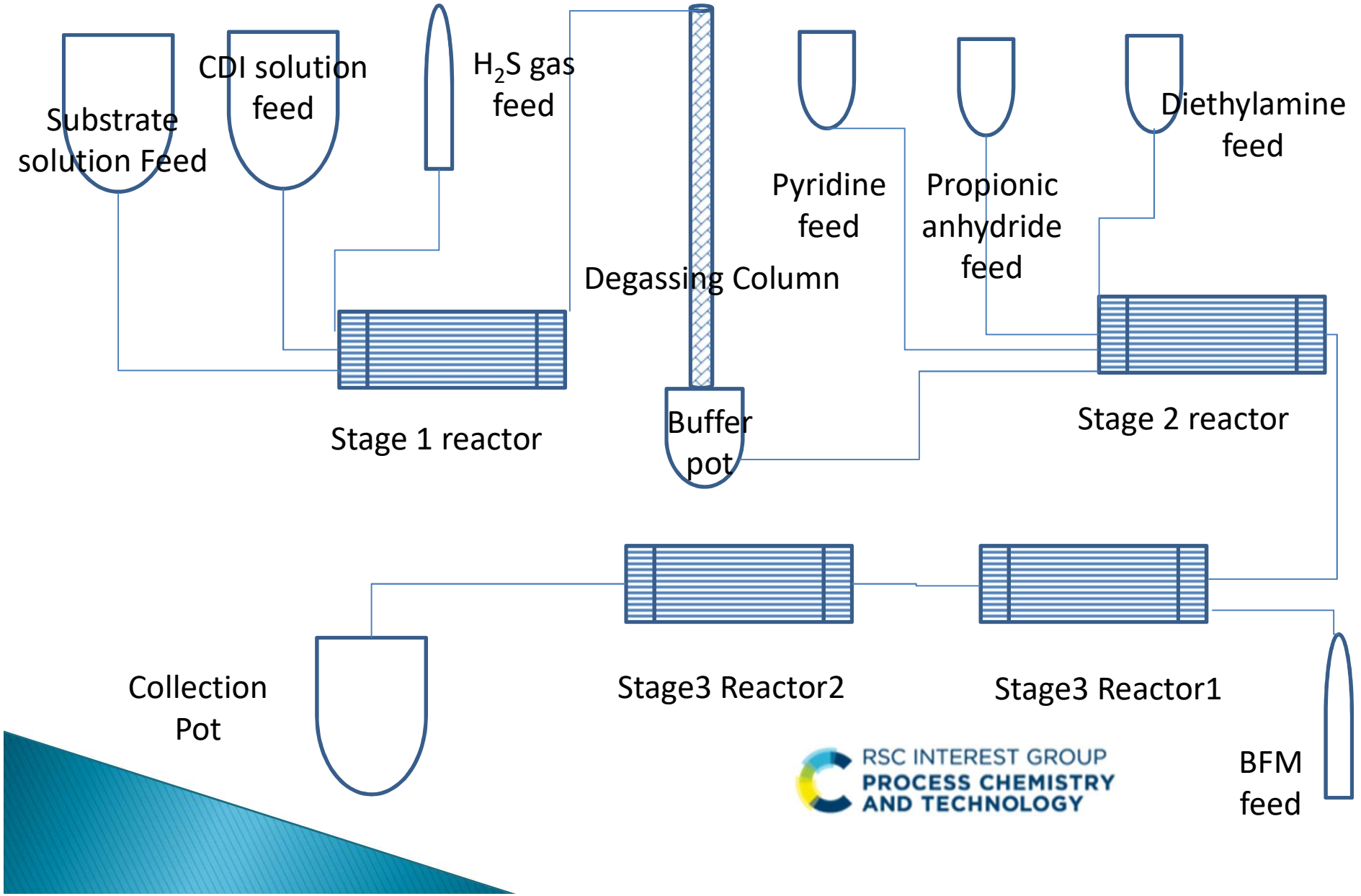
Telescoped vs multistage flow

- Able to run in process checks and take corrective action eg stir for longer add more reagent prior to moving to next step.

- Process can be monitored continuously but unable to correct material that has already moved on. Each step is segregated stage 1 reactor never sees stage 3 so less risk of contamination

Telescoped	Multi stage flow

Process Schematic



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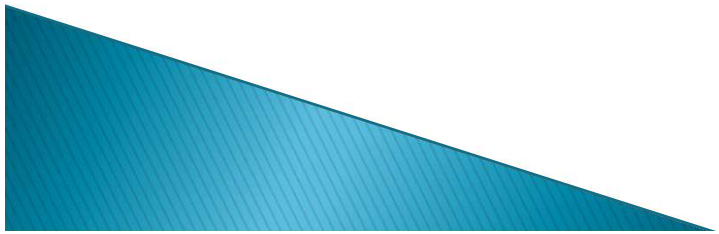
Process Optimisation and Design Space Definition

- Both multistage flow processes and telescoped batch processes suffer from too many variables.
- This process has 9 flow rates 4 reactor temperature, 2 solution feed concentrations and a buffer pot fill level 16 parameters in all.
- A large part of this must be reduced by process understanding as the experimental demand is just too large to explore the whole design surface.

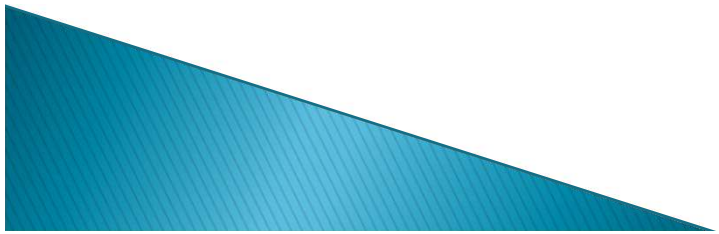


Summary

- Avoiding solids will make your process easier but be prepared to see them at unexpected moments.
- In developing a flow process you will have to change your mindset on what constitutes an independent variable.
- A good undertanding of the reaction kinetics and impurity profile over the whole process is essential.
- Incomplete earlier steps are going to be your main route to failure. Design with this in mind! Ensure your analytical methods can cope with this.

Acknowledgements

- All my colleagues “Chemists, Analysts and Engineers” over the years who delivered this process.
- Scale up systems whose software and support underpinned the kinetic understanding of this process



Q and A